REMARKS/ARGUMENTS

Claims 3-4, 7-9, 12-14 and 16-23 are pending in this application and presented for examination. Claims 22 and 23 are newly added. Reconsideration is respectfully requested.

I. SUPPORT FOR NEW CLAIMS

Claims 22 and 23 find support throughout the specification as originally filed. More particularly, support for claim 22 is found, for example, on page 16, line 18, bridging to page 17, line 30. Support for claim 23 is found, for example, on page 18, line 19, bridging to page 19, line 12 and continuing on page 19, line 15 and bridging to page 21, line 11. Thus, no new matter has been introduced and Applicants respectfully request that the claims be entered.

II. THE INVENTION

The present invention pertains *inter alia*, to novel means for averting undesirable pharmacokinetic (drug) interaction between a drug and a concomitant drug(s) *in vivo* in humans (*see*, page 1, lines 8-11 of the specification). As the means of averting such undesirable drug interactions, the present invention provides an innovative drug delivery system that controls the *in vivo* release time and/or the release site of the drug.

III. FIRST REJECTION UNDER 35 U.S.C. § 103

Claims 3-4, 7-9, 12-14, and 16-17 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 4,891,223 ("Ambegaonkar *et al.*"). In the Office Action dated March 12, 2002, the Examiner alleges that Ambegaonkar *et al.* disclose a controlled release delivery coating formulation for bioactive substances. According to the Examiner, Ambegaonkar *et al.* teach a composition which comprises a bioactive core, which can be 100% active substance or could be an admixture with an inert binder or substrate. The core has two coatings which can control the release of the active core. The Examiner acknowledges

that the reference does not teach the specific drug as claimed. In response, Applicants respectfully traverse the rejection.

As the Examiner is well aware, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the reference itself or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Ambegaonkar *et al.* teach the factors to obtain a zero-order release pattern by modifying the thicknesses of the first and second coatings and the composition of the second coating (*see*, column 5, lines 49 to 58, column 17, lines 53 to 65 and column 19, lines 11 to 28), as well as disclosing the dissolution profiles of Example preparations in Figures 5 to 11. The dissolution profile shown in Figures 5 to 10 gives zero-order, first-order, fractional-order, or biphasic release (*see*, column 1, lines 8 to 12 and column 5, lines 49 to 53). Because these preparations begin to release the drug ***just after*** they contact with fluids in the digestive tract, when taken with a concomitant drug, the preparation and the concomitant drug reach a drug-metabolizing enzyme in the liver at **the same time**, and cause drug interaction. Accordingly, the preparations disclosed in Ambegaonkar *et al.* cannot achieve averting drug interaction as taught and claimed in the present invention.

Claim 3 of the present invention sets forth:

> A system for averting undesirable drug interaction between a drug and concomitant drug(s), both of which are metabolized by the same molecular species of drug-metabolizing enzyme in humans, or between a drug and concomitant drug(s) that is metabolized by the molecular species of drug-metabolizing enzymes that is inhibited by the said drug, which comprises **timed-release control** of the said drug or **control of the site of release** of the said drug to the digestive tract.

As is taught and claimed in the present invention, it is possible to prolong release of a drug using **time release control** after the preparation has been taken. By the complete delay of release, there is **no competition with the concomitant drug** over a drug-metabolizing enzyme and drug interaction can be averted. Another means for adverting an undesirable drug

interaction in the present invention, is the **specific release** preparation in the lower digestive tract which also averts competition with a concomitant drug over a drug-metabolizing enzyme.

The Examiner's attention is respectfully directed to Figure 1 of the present specification. As is shown in Figure 1, the dissolution profile of the ***timed-release control*** preparation used for the present invention is completely different from the cited art. As indicated therein, the preparation begins release of drug **at a specific time** (*e.g.*, 4 hours) after it contacts with fluids in the digestive tract and releases drug immediately. In the present invention, it is necessary to prolong release of the drug for a certain time after the preparation has been taken. By delaying the release, there is **no competition** with the concomitant drug over a drug-metabolizing enzyme and the drug interaction can be averted. Another means for the present invention, the lower digestive tract specific release preparation also can avert competition with a concomitant drug over a drug-metabolizing enzyme.

Again, it is possible to prolong release of a drug using **time release control** after the preparation has been taken. By the complete delay of release, there is **no competition with the concomitant drug** over a drug-metabolizing enzyme and the drug interaction can be averted.

For example, as discussed on page 16, line 18, bridging to page 17, line 30, a variety of time-release control technologies can be used. Timed-release control is technology wherein the time until a drug **begins to be released** after it has been taken is prolonged for a certain time (*e.g.* 4 hours, *see* Figure 1). This has the mechanism of initiating release of the drug in the preparation by extending the time when it comes into contact with the water content of the digestive tract and in further detail, technology of the following types have been developed (Gekkan Yakuji, 41(6), 35-38, 1999/Igaku no Ayumi, 178(8), 441-444, 1996).

> ***① Insoluble membrane bursting-type***
>
> These are preparations where the drug and swelling agent are coated with a membrane that is insoluble in water. The water content penetrates the insoluble membrane to reach the inside, the inside swells, and the insoluble membrane at the surface bursts under pressure so that the drugs inside are exposed to outside liquid. ***The time until the water permeates and the inside swells so that the membrane ruptures determines the time when drug release begins.***

Examples are the TES (time-controlled explosion system) of Fujisawa Yakuhin Co., Ltd. (Pharm. Tech. Japan, 4, 1415-1422, 1988) and the prolonged release tablets of Tanabe Seiyaku (*Chem. Pharm. Bull*, 11, 3036-3041, 1992), whereby a core tablet made of swelling disintegrator is compressed into a tablet with a substance with low water permeability.

② Cap breakaway-type

This is an insoluble capsule filled with drug having a stopper made from a hydrophilic polymer. When water swells the hydrophilic plug and the cap can no longer remain in the opening in the capsule and flips off, the drug inside the capsule comes into contact with outside liquid and is released. ***The time until the cap flips off determines the time for which release of the drug is prolonged.*** The Pulsincap of Scherer DDS (*Pharm. J.*, 247, 138, 1991), etc., are given.

③ Membrane permeation increasing-type

The preparation is drug and organic acid inside a resin layer comprising cationic groups. ***The water content penetrates the resin layer, the organic acid inside is dissolved, and the acid and cationic groups of the resin interact, resulting in an increase in penetrability of the resin and release of the drug.*** The granules of Tanabe Seiyaku (*Maku* 19, 392-399, 1994) comprising Eudragit RS as the outer layer and organic acid and drug as the inner layer, etc., are given.

④ Hydrogel layer dissolving-type

This is a preparation of drug encapsulated by hydrophilic polymer. The water content soaks into the hydrophilic polymer, the polymer gel is gradually dissolved, and the drug inside comes into contact with outside liquid and is released. ***The gel shape and gel dissolution determine the time for which release of the drug will be prolonged.*** The chronotropic DDS coated with a hydroxypropyl methyl cellulose layer of Milano University (*Eur. J. Pharm. Biopharm*, 40, 246-250, 1994) and tablets of Kumamoto University (*Chem. Pharm. Bull.*, 43, 311-314, 1995) whereby hydroxyethyl cellulose is compressed into the core tablet containing drug are given as examples. Furthermore, the applicant developed as an improved form a tablet with a core, which is obtained by compression molding a hydrophilic base and a hydrogel-forming polymer substance together with a core tablet containing drug. This preparation can be used as a drug delivery system for averting undesirable interaction between multiple drugs metabolized by the

> drug-metabolizing enzyme CYP3A4. This preparation preferably is a combination of a freely erodible filler mixed in the core tablet containing drug in order to completely dissolve or suspend the drug before drug release begins.

These **time release control** technologies are simply not taught or suggested in the cited art. As can be seen from the four exemplified technologies, the time at which the drug release will be prolonged is known or can be easily calculated or measured. The formulations have an architecture which will allow the calculation of when the drug will be released. For instance, in ① above, "***[t]he time until the water permeates and the inside swells so that the membrane ruptures determines the time when drug release begins.***" This is an example of what is meant by "**time-release control**" as is currently taught and claimed.

Further, the present invention provides methods for controlling release in the lower digestive tract. Controlling release in the lower digestive tract is technology for controlling initial release of the drug until the preparation has reached the lower digestive tract, such as the ileum and/or colon, etc., after being taken. It has the mechanism of releasing the drug in the environment of the lower digestive tract.

For example, as set forth on page 18, line 19, bridging to page 19, line 12 and continuing on page 19, line 15 and bridging to page 21, line 11:

> The ileum and colon have more bacteria than the stomach or upper small intestine and therefore, by coating the drug with a polymer that is decomposed by bacterial enzymes, the drug is not released in the stomach or upper small intestines. ***The polymer at the preparation surface is decomposed and dissolved and the drug is released after reaching the ileum and/or colon.*** Systems whereby azo aromatic polymers are decomposed by the azo reductase of intestinal flora of the University of Ohio (*Science* 233, 1081, 1986) and the University of Utah (*Pharmaceutical Research*, 9(12), 1540-1545, 1992), systems whereby polysaccharides are decomposed by the β-galactosidase of intestinal flora of Freiburg University (*Pharmaceutical Research* 10(10), S218, 1993), and systems of decomposition by chitosanase using chitosan of Teikoku Seikayu (Japanese Patent No. Hei 4(1992)-217924) are given. A system that uses a lectin-type substance present in the large intestines of the University of Utah (*Proc. Int. Symp. Control.. Rel. Bioact. Mat.*, 17, 130-131, 1990) is also reported.

Furthermore, there is also the system of the applicants (International Disclosure No. 95/28963) whereby organic acid is generated using intestinal bacteria and as a result, the film covering the drug is dissolved by said organic acid without affecting pH of the nearby cecum and the drug is ***specifically released to a site in the colon***. In concrete terms, it is a system for specific release of drug in the colon of the digestive tract consisting of drug that is coated with a polymer that is dissolved by an organic acid and a saccharide that quickly generates an organic acid as a result of reaction with intestinal flora in the lower digestive tract.

A system for averting drug interaction that uses the drug delivery system of the present invention will now be explained based on the type of drug interaction.

(a) System for averting interaction in terms of drug metabolism

In general, when multiple drugs that are metabolized by a drug-metabolizing enzyme of the same molecular species compete for a metabolizing enzyme in the liver, metabolism of the drug that has inferior affinity for the metabolizing enzyme is inhibited and interaction in the form of a rise in the blood concentration and prolonged blood half life is seen. In addition, when a drug that is metabolized by a certain drug-metabolizing enzyme and a drug that interferes with the same metabolizing enzyme are both present in the liver, metabolism is inhibited and interaction in the form of a rise in the blood concentration and prolonged blood half life is seen. Consequently, competition with concomitant drugs over a drug-metabolizing enzyme can be averted by controlling the release time so that a drug will reach the drug-metabolizing enzyme in the liver a specific time after a concomitant drug has been absorbed. ***Moreover, competition over a drug-metabolizing enzyme can be averted by releasing a drug specifically in the lower digestive tract and thereby staggering the time when concomitant drugs reach the liver.***

In addition, CYP3A4 accounts for more than half of drug metabolism by CYP and as much as 80% of the amount distributed to the liver is also distributed to upper small intestines consisting of the duodenum and jejunum. Therefore, when a drug metabolized by CYP3A4 is orally administered, it is metabolized at the epithelium of the small intestines before it is absorbed from the digestive tract. Consequently, competition over CYP3A4 in the upper small intestines can be averted

by (1) delaying the drug release time using timed-release control technology, which should avert coexistence of at the site of metabolism of concomitant drugs (epithelium of the small intestines and liver) or (2) by releasing the drug in the ileum and colon in which little CYP3A4 is distributed using technology for controlling release specifically in the lower digestive tract.

For instance, inhibition of midazolam metabolism due to competition with conivaptan and the rise in the blood concentration that accompanies the same can be averted by administration with a timed-release preparation with which release of the conivaptan in the digestive tract is delayed by as much as 2 hours, as shown in the examples and test examples given later.

(b) System for averting interaction in terms of drug absorption

Interaction involving absorption of drugs occurs mainly in the digestive tract with oral administration and is the result of an effect on solubility and permeability of the intestinal epithelium due to a change in gastric pH. ***In concrete terms, drug interaction can be averted by (1) timed-release control whereby a drug reaches the site of the digestive tract in question once absorption of concomitant drugs from the digestive tract has been completed or (2) by technology for controlling the site of release site whereby the site in the digestive tract at which concomitant drugs are absorbed is avoided.***
For instance, a reduction in the plasma concentration of cefadroxil due to competition between cefadroxil and cephalexin over a carrier can be averted by administration with a timed-release preparation with which release of the cephalexin is delayed by as much as 3 hours.

(c) System for averting interaction in terms of drug distribution

Interaction involving drug distribution usually occurs with competition over a protein in the blood. Drug interaction in the blood can be averted by timed-release control or releasing a drug specifically in the lower digestive tract so that it reaches the blood after the blood concentration of concomitant drugs has dropped to a certain point.
For instance, inhibition of binding of acetohexamide with blood proteins induced by aspirin and a rise in the free acetohexamide concentration of the blood and hypoglycemic symptoms that accompany the same can be averted by controlling liberation of acetohexamide from blood proteins as a result of administration of aspirin with a timed-release preparation with which release in the

digestive tract is delayed by as much as 4 hours after oral administration.

(d) System for averting interaction in terms of drug excretion

Interaction involving drug excretion often occurs due to competition over a carrier in the uriniferous tubules. ***Interaction in the uriniferous tubules can be averted by timed-release control or release of a drug specifically to the lower digestive tract so that a drug reaches the kidneys once excretion of concomitant drugs from the uriniferous tubules has been completed for the most part.***
For instance, a reduction in renal excretion as a result of inhibition of secretion of procainamide via the uriniferous tubules induced by competition from cimetidine and an increase in the blood concentration that accompanies the same can be averted by oral administration with a timed-release preparation with which release of procainamide in the digestive tract is delayed by as much as 4 hours so that inhibition attributed to competition over secretion from the uriniferous tubules is controlled.

The system for averting drug interaction of the present invention can include other technology as long as the *in vivo* release time and/or release site of 1 or multiple drugs is controlled.

Again, the present invention provides *inter alia*, a system for averting undesirable drug interaction between a drug and concomitant drug(s), both of which are metabolized by the same molecular species of drug-metabolizing enzyme in humans, or between a drug and concomitant drug(s) that is metabolized by the molecular species of drug-metabolizing enzymes that is inhibited by the drug, which comprises **control of the site of release** of the drug to the digestive tract.

For example, a-d above illustrate controlling the site of release of the drug to the digestive tract in terms of drug metabolism, drug absorption, drug distribution, and in terms of drug excretion. These technologies are simply not taught or suggested in the prior art. As can be seen from the four exemplified technologies, the site of release is known or can be easily calculated or measured. These formulations have an architecture which will allow the calculation of where the drug will be released.

In contrast, Ambegaonkar *et al.* relate to a bioactive composition having a sustained release delivery pattern when contacted with a suitable surrounding media comprising (a) a bioactive material core, (b) a first coating enveloping the bioactive material core, and (c) a second coating enveloping the first coating, whereby when the composition is exposed to the surrounding media, the exposure will result in the controlled release of the bioactive material (*see*, column 19, lines 37, and column 20, line 12, Ambegaonkar *et al.*). The drug delivery system disclosed in Ambegaonkar *et al.* releases drugs continuously, preferably at a uniform rate. At no point do Ambegaonkar *et al.* teach anything about a system to avert undesirable pharmacokinetic (drug) interaction. Further, there is no teaching in Ambegaonkar *et al.* to avert the undesirable pharmacokinetic (drug) interaction between a drug and concomitant drugs(s).

Therefore, Applicants respectfully request that the Examiner withdraw the rejection.

IV. SECOND REJECTION UNDER 35 U.S.C. § 103

The Examiner rejected claims 18-21 as allegedly being obvious under 35 U.S.C. 103(a) over Ambegaonkar *et al.* (U.S. Patent No. 4,891,223). In response, Applicants respectfully traversed the rejection.

Ambegaonkar *et al.* does not teach or suggest any system, method or mechanism for averting undesirable drug interaction between a drug and concomitant drug. The drug delivery system disclosed in Ambegaonkar *et al.* releases drugs continuously, preferably at a uniform rate.

In the present invention, it is possible to prolong release of a drug using **time release control** after the preparation has been taken. By the complete delay of release, there is no competition with the concomitant drug over a drug-metabolizing enzyme and the drug interaction can be averted. Claim 18 recites the system for averting undesirable drug interaction between a drug and concomitant drug, wherein the drug and the concomitant drug are both metabolized by the same molecular species of **drug-metabolizing enzyme** (*e.g.* CYP3A4). There is absolutely no teaching or suggestion of a drug metabolizing enzyme in Ambegaonkar *et al.* As obviousness can only be established by modifying the teachings of the prior art to

produce the claimed invention where there is some teaching, suggestion, or motivation to do so, Ambegaonkar *et al.* do not make the instant invention obvious

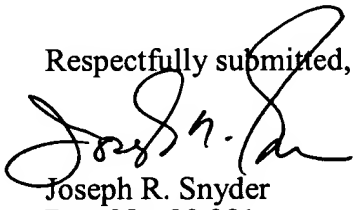
Therefore, Applicants respectfully request that the Examiner withdraw the rejection.

V. CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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